USARIEM Technical Report No. T-01/18

WOMEN AT ALTITUDE: EFFECT OF MENSTRUAL-CYCLE PHASE ON ACUTE MOUNTAIN SICKNESS DURING DEPLOYMENT TO HIGH ALTITUDE TERRAIN

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Technical Report

4. TITLE AND SUBTITLE

Women at Altitude: Effect of Menstrual-Cycle Phase on Acute Mountain Sickness During Deployment to High Altitude Terrain

5. FUNDING NUMBERS

6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER

T-01/18

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Ft. Detrick, MD 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; Distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The physiologic responses to the cyclic fluctuations in ovarian steroid hormones associated with the menstrual cycle in women are well known to affect certain disease states and could alter responses to environmental stressors. Rapid deployment to high mountain terrain induces acute mountain sickness (AMS), which can be an important source of performance decrements and Disease and Non-Battle Injury loss of personnel in military units. To determine the effect of menstrual cycle phase on the occurrence of AMS, symptoms were assessed in 39 women aged 18 to 33 years with normal menstrual cycles who were exposed to 4300 m altitude continuously on the summit of Pikes Peak, CO for 12 days or in a hypobaric chamber for 60 hours during the early follicular (follicular phase group) or luteal phase (luteal phase group) of their menstrual cycle. The clinical course of AMS in these women was similar to that reported previously in men. Overall, more than 60% of the women in this study experienced AMS during the first 24 hours of altitude exposure. There were no statistically significant differences between symptom scores of the follicular and luteal phase groups. However, the prevalence of AMS was slightly lower in the luteal phase compared to follicular phase volunteers. We conclude that effects of menstrual cycle phase are too small to be of practical significance for most women involved in military operations or civilian recreational pursuits at altitudes up to 4300 m.

14. SUBJECT TERMS

altitude illness, hypoxia, women, menstrual cycle, progesterone, estradiol, luteal, follicular

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unclassified

USARIEM TECHNICAL REPORT T-01/18

WOMEN AT ALTITUDE: EFFECT OF MENSTRUAL-CYCLE PHASE ON ACUTE MOUNTAIN SICKNESS DURING DEPLOYMENT TO HIGH ALTITUDE TERRAIN

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October 2001

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BACKGROUND

In 1994 the United States Congress directed that research on health and performance of military personnel sponsored by the Department of Defense (DOD) should include women and apportioned funds to facilitate studies of women serving in armed forces. To distribute the funding effectively, the DOD established the Defense Women's Health Research Program (DWHRP) with the U.S. Army Medical Research and Material Command (MRMC) serving as the managing and coordinating agency (Davis and Woods, 1999). At the request of MRMC, the Institute of Medicine of the National Academy of Sciences convened a committee of experts to evaluate what was known about health issues of military women and recommend areas for research. The resulting report documented that little was known about the health and performance of military women and recommended specific areas for increased research attention. Adaptation to environmental stressors by women was one of the areas that was identified as needing more research (Committee on Defense Women's Health Research, 1995).

Exposure to high terrestrial altitude is an environmental stressor which women may encounter in military service. In 1995 a collaborative research group from University of Colorado Health Sciences Center in Denver, CO and the Palo Alto Veterans Affairs Health Care System in Palo Alto, CA was awarded a DWHRP grant (#DAMD17-95-C-5110) for a three year study of the role of the alpha-adrenergic nervous system as a possible mediator of altitude acclimatization in women deployed to high terrestrial altitude. The Thermal and Mountain Medicine Division (TMD) of the US Army Research Institute of Environmental Medicine (USARIEM) participated in the collaborative studies in accordance with TMD's mission to determine means to sustain military personnel deployed in mountain environments. The TMD research effort was specified under MRMC Scientific and Technical Objective (STO) J - Sustainment in Mountainous Terrain, Task JA - Quantify influences on inherent soldier characteristics and physiological status on military performance in mountainous terrain. The series of studies included in this collaborative effort were conducted during the spring and summer months of 1996 through 1998 in the Geriatric Research, Education and Clinical Center (GRECC) at the Veteran's Affairs Palo Alto Health Care System, Palo Alto, CA; the Hypobaric Chamber Facility at USARIEM, Natick, MA; and the USARIEM John Maher High Altitude Research Laboratory on the summit of Pikes Peak, CO.

ACKNOWLEDGMENTS

Ms. Jacinda Mawson, Ms. Beth Beidleman and Ms. Leslie Levine are thanked for their substantial contributions to the recruitment of volunteer test subjects. The nursing and dietetics staff at the Aging Study Unit and Clinical Laboratory of GRECC are thanked for their participation and support during the sea-level studies in 1996 and 1998. The acting head of the of the Hypobaric Chamber, MSG Mark Sharp; the Hypobaric Chamber Crew Chiefs, Mr. Richard C. Langevin, Mr. Vincent A. Forte, Jr., and SSG James R. Moulton; and the Hypobaric Chamber Operators at USARIEM are thanked for safe and efficient operation of the hypobaric chamber during the sea-level and altitude studies in 1997. SSG James R. Moulton, SGT James L. Kenney, SGT Douglas Zamistil, SSG Tayfield Reid, Mr. Eric Lammi, Ms. Debra Hensmen, Ms. Ingrid Asmus, Ms. Jacinda Mawson, Ms. Shannon Dominick, LTC William Bell, LTC Ronald Jackson and LTC Patricia A. Young are thanked for their participation in data collection and support activities during various portions of the study. Finally, profound gratitude is extended to the volunteer test subjects for their excellent cooperation, extraordinary efforts and dedication in completing the many and often difficult studies included in all phases of the project.

Major funding for the project reported here came from DWHRP Extramural Grant #DAMD17-95-C-5110 entitled "Women at altitude: Effects of menstrual cycle phase and alpha-adrenergic blockade on high-altitude acclimatization." Additional funding was from DWHRP Intramural Grant #DI950050 entitled "Effect of menstrual cycle phase on muscle fatigue and physical performance during altitude acclimatization."

EXECUTIVE SUMMARY

Women currently constitute a conspicuous proportion (up to 20%) of the active duty and reserve component US military forces and are deployed worldwide. The physiologic responses to the cyclic fluctuations in ovarian steroid hormones associated with the menstrual cycle in military-aged women are well known to affect certain disease states (Case and Reid, 1998) and could also alter responses to environmental stressors (Norwood and Ursano, 1997). Little is known about specific effects of ovarian hormone fluctuations on responses to environmental conditions encountered by military women in operational environments, however.

Rapid deployment to high mountain terrain induces acute mountain sickness (AMS), which can be an important source of performance decrements and Disease and Non-Battle Injury (DNBI) loss of personnel in military units (Cymerman and Rock, 1994). Acute mountain sickness (AMS) is caused by the hypobaric hypoxia that is ubiquitous at high altitude and usually resolves as the body adapts to low oxygen levels through the process of altitude acclimatization (Johnson and Rock, 1988). Changes in the process of altitude acclimatization associated with ovarian steroid hormone fluctuations could alter the incidence and severity of AMS in military women deployed to high altitude during different phases of their menstrual cycle, but there is insufficient information available in the scientific and medical literature to ascertain the existence, size or clinical impact of this theoretical effect.

To determine the effect of menstrual cycle phase on the occurrence of AMS, symptoms were assessed in 39 women aged 18 to 33 years with normal menstrual cycles who were exposed to 4300 m altitude continuously on the summit of Pikes Peak, CO for 12 days or in a hypobaric chamber for 60 hours during the early follicular (follicular phase group) or luteal phase (luteal phase group) of their menstrual cycle. The clinical course of AMS in these women as detected by standard questionnaires and clinical assessment (Environmental Symptoms Questionnaire [ESQ] and the Lake Louise AMS Scoring System [LLS]) was similar to that reported previously in men and the few women who have been previously studied on Pikes Peak, i.e., symptoms were most frequent and severe early in the exposure, then decreased or resolved completely. Overall, more than 60% of the women in this study experienced AMS during the first 24 hours of altitude exposure.

There were no statistically significant differences between symptom scores of the follicular and luteal phase groups. The overall severity of AMS symptoms determined using an index derived from the ESQ scores was lower in the luteal phase group after the first 24 h of exposure, but the difference was not statistically significant. The prevalence of AMS (ratio of the number of individuals with AMS divided by the number in the exposed group) was lower in the luteal phase compared to follicular phase volunteers, and that difference, was statistically significant for the ESQ, but not LLS criterion. The effect was small (<15%), however.

Based upon the results of this study we conclude that effects of menstrual cycle phase are too small to be of practical significance for most women involved in military operations or civilian recreational pursuits at altitudes up to 4300 m.

INTRODUCTION

The field environment is often the primary workplace for deployed military personnel. In the field, adverse climatic and terrain features constitute occupational hazards for the deployed soldiers. Just as occupational hazards in commercial and industrial workplace settings can impact both the individual worker and the organization that employs that worker (via loss of productivity, loss of trained expertise, etc), the hazards of the soldier's field environment workplace can threaten both the well-being of individual soldier and the mission of the unit to which that soldier belongs. The first step to lessen the potential impact environmental hazards in the field is to compile an accurate understanding of those features of the specific environment which threaten the soldier. Such an understanding facilitates the development of effective counter measures and allows the tactical commander to plan for potential force decrements from the environment hazards.

In mountainous regions at moderate to high altitude, i.e., regions over 1500 m (~5000 ft), the decreased partial pressure of oxygen in ambient air is a ubiquitous environmental hazard which degrades physical and mental performance, and causes a variety of pathological conditions known as "altitude illnesses" in sojourners from lower elevations. Acute mountain sickness (AMS) is the most common altitude illness and is an important source of performance decrements and Disease and Non-Battle Injury (DNBI) manpower loss in military units rapidly deployed to mountain regions (Dusek and Hansen, 1969; Pigman and Karakla, 1990; Singh et al., 1969).

The extent to which any person is affected by AMS is a function of both individual susceptibility and the magnitude of hypobaric hypoxia (decreased tissue oxygenation due to lower barometric pressure) that is induced by the combination of speed of ascent and altitude achieved (Johnson and Rock, 1988). Gradual and/or chronic exposure to high mountain altitudes allows physiologic adaptation to fairly severe levels of hypobaric hypoxia through the process of 'altitude acclimatization.' Acclimatization is the result of a series of integrated changes in physiology which facilitate maximum body function for the amount of oxygen in the ambient air (Young and Young, 1988). A well-acclimatized state is characterized by increased performance relative to the unacclimatized condition and by the absence of AMS and other altitude illnesses (Young and Young, 1988; Johnson and Rock, 1988).

Women are a significant proportion of the active duty and reserve component personnel of the US military forces and are subject to world-wide deployment (Committee on Defense Women's Health Research, 1995; Davis, 1999), including deployment to mountainous regions. In pre-menopausal women, the cyclic fluctuations of ovarian steroid hormones associated with menstrual-cycle phase changes influence many physiological processes and exacerbate some chronic disease conditions (Case and Reid, 1998). These hormone fluctuations can affect some of the pivotal physiologic processes that mediate altitude acclimatization, including ventilatory control (Bayliss and Millhorn, 1992; Lyons

1976) and fluid/volume regulation (Chapman et al., 1997; Fortney et al., 1988). If hormone fluctuations during the menstrual-cycle are sufficient to alter the course of early altitude acclimatization, the effect should be evident as differences between menstrual cycle phases in the occurrence of AMS and other 'markers' of acclimatization. Whether such differences actually exist has not been established.

There have been many observations of AMS and altitude acclimatization in women reported in the scientific and medical literature. However, prior to beginning this investigation, there appeared to be no reports of the effect of menstrual cycle phases on AMS and altitude acclimatization. Instead, the research usually compared women to men, often by using historical data, but occasionally with direct comparisons in a single study. The idea that menstrual cycle phase might influence acclimatization was implicit in these comparisons of men and women, for the underlying (although often unstated) assumption appears to have been that any differences between men and women would be due largely to the physiologic effects of the hormones that drive the menstrual cycle.

Results of early studies of ventilatory parameters and other aspects of the physiology of altitude acclimatization in women (Campbell and Hoagland, 1901; Cudkowicz et al., 1972; FitzGerald, 1913; Hannon et al., 1966, 1969,1975,1976) were interpreted to suggest that women acclimatize to high altitude at least as well, if not better, than men (Hannon, 1978). However, observations of AMS in women, when compared to men, have not been consistently in favor of women acclimatizing as well or better than men. When compared to selected historical controls, women often did appear to be less susceptible to AMS than men. On the basis a query of experienced practitioners in Peru, Fitzmaurice, (1920) suggested that women suffered less AMS then men, but suggested that they did so partially because women lead a less "strenuous life" than males and were more "abstemious in their habits." Acute mountain sickness symptoms measured in eight young women living on the summit of Pikes Peak for 10 weeks, when compared to AMS symptoms in males on Pikes Peak in separate studies, suggested that women possibly are less susceptible to AMS (Hannon, et al., 1976; Harris, 1966). Likewise, Krámar and colleagues (1983) felt that the AMS they observed in seven women climbers on Ana Purna in the Himalayan mountains was less severe than that reported in 12 soldiers on Pikes Peak in Colorado (Kobrick and Sampson,1979). They suggested that the difference could have been due to a slower ascent rate for the women, but also suggested that women may have less frequent or intense symptoms than men (Krámar et al., 1983).

When the occurrence of AMS was compared directly between women and men in the same study, the reported results do not show a consistent pattern. For example, during a two-month study on the summit of Pikes Peak in which he and his wife served as their own test subjects, Grollman (1930) observed that his wife experienced AMS symptoms while he did not. (Grollman and his wife were married shortly before beginning the study on Pikes Peak, and the study apparently served as their 'honeymoon.') In a much larger study of individuals attending conferences at moderate to high elevations in Colorado, Honigman et al. (1993) found a higher incidence of AMS in 981 women compared to 2,177

men, a finding that would suggest a possible adverse effect of menstrual cycle hormones. However, possibly half of the women studied were old enough to be postmenopausal and would not be expected to be affected by ovarian hormone fluctuations. Other investigators have reported that the differences in the incidence of AMS between sexes in trekkers and mountain climbers were small and lacked statistical significance (Hackett et al., 1976; Maggiorini et al., 1990; Roach et al., 1998), although Maggiorini and colleagues stated that males experienced the "more serious forms" of altitude illness such as cerebral and pulmonary edema.

Finally, there are a large number of studies of AMS reported in which both sexes were studied together without differentiating between them (e.g., Hackett et al., 1982; Dean et al., 1990; Anholm et al., 1979; Montgomery et al., 1989). The implicit assumption in the design of these studies was that AMS does not differ between men and women. That assumption was not always explicitly stated, however, and may not be justified based upon the equivocal evidence reported in the literature.

Since the beginning of the series of studies reported here, the results of another study in which the occurrence of AMS was compared between menstrual cycle phases has been reported in abstract form (Riboni et al., 1999). That study did not find statistically significant differences in incidence of AMS, symptoms scores, or arterial oxygen saturation between the mid-follicular and the luteal menstrual-cycle phases in 17 women during a 12-hour exposure to 426 mmHg (~4800 m/15,000 feet altitude) in a hypobaric chamber using a cross-over study design (Riboni et al., 1999). Additionally, there were no statistically significant differences in those same parameters between the women in their mid-follicular phase and 17 males exposed at the same time.

While the findings of Riboni et al. may be stronger evidence against an effect of menstrual cycle phase on AMS in women than has been previously reported, the results cannot be considered either definitive or necessarily relevant to a military deployment scenario. The study used a rapid ascent rate characteristic of chamber flights and a relatively high altitude, the combination of which caused a stronger hypoxic stimulus than would be normally encountered in operational scenarios. Because the occurrence of AMS is more-or-less linearly related to the degree of hypoxia (Johnson and Rock, 1988), the stimulus may have been strong enough to obscure any effect of increase in ventilation due to menstrual-cycle related hormones. Additionally, the 12-hour observation period did not allow evaluation of the resolution of AMS symptoms, a traditional measure of the efficiency of acclimatization. Finally, as with all initial findings, the results should be replicated before they can be widely accepted.

In summary, it is not possible to determine from the literature whether the menstrual cycle phase during which a women is exposed to high altitude has an effect upon altitude acclimatization and the occurrence of AMS. The purpose of the investigations reported here was to determine if altitude acclimatization in pre-menopausal women is affected by the phase of the menstrual cycle during which they ascend. The occurrence of AMS

symptoms and time course of symptom resolution was used as an integrated indicator of effective altitude acclimatization. Based upon the well documented phenomenon of ventilatory stimulation due to increased progesterone levels during the luteal phase of the menstrual cycle (see Muza et al., 1997 for review) we hypothesized that women volunteer test subjects exposed to 4300 m altitude during the luteal phase of their menstrual cycle would maintain higher arterial oxygen saturation and, consequently, experience less AMS relative to those exposed during the follicular phase of their cycle. In essence, we hypothesized that women in the luteal phase of their menstrual cycle would be to some degree preacclimatized to altitude relative to women in the follicular phase of their cycles. Additionally, we hypothesized that the time course to resolution of AMS symptoms would be more rapid in those women who develop AMS during the luteal phase compared to women in the follicular phase of their menstrual cycle, indicating more rapid altitude acclimatization during the luteal phase.

OBJECTIVE

The primary objective of the investigation was to measure symptoms of AMS in young women exposed to 4300 m altitude for periods of 52 hours to12 days beginning in either the follicular or luteal phase of their menstrual cycle as a means to determine the incidence, severity, and time course of AMS relative to menstrual cycle phase. Secondary objectives included relating AMS to ovarian hormone levels, ventilation, and oxygen saturation measured by pulse-oxymetery.

METHODS

The potential effect of menstrual cycle phase on AMS and altitude acclimatization was examined in a series of three studies performed during 1996-1998. Each study used a prospective trial design in which AMS symptoms, resting ventilation and arterial oxygen saturation were evaluated first at sea level (SL) and then at high altitude (HA) in two groups of women volunteer test subjects, one exposed to SL and HA in the follicular phase (FOL) and the other in the luteal phase (LUT) of their menstrual cycles. The studies were single-blind for the independent variable of menstrual cycle phase (i.e., the investigators collecting symptom data were unaware of the volunteer's menstrual cycle phase) and unblinded for altitude. They were part of a larger project designed to delineate the role of menstrual cycle phase and activation of the α-adrenergic nervous system in mediating various aspects of altitude acclimatization in women (Moore, 1999). Within the context of the larger project, the investigation of AMS and acclimatization reported here was accomplished by limiting the evaluation to untreated volunteer subjects (1996) and to volunteer subjects in the placebo-treatment arm of the project (1997, 1998). Additionally, the data from the individual study years were analyzed in two different combinations (1996+1997+1998 and 1996+1998) to allow evaluation of both the initial occurrence and the subsequent resolution of AMS as an integrated measure of altitude acclimatization (see "Altitude Exposure," below). The overall project and individual study year protocols were approved by the institutional review boards (IRBs) at Stanford University (the IRB for

the Palo Alto VA Health Care Systems), the University of Colorado Health Sciences Center, the US Army Research Institute of Environmental Medicine, and the Surgeon General of the Army's Human Subjects Research Review Board.

VOLUNTEER TEST SUBJECTS

A total of 52 women participated in the overall DWHRP-funded project. Five women voluntarily withdrew from the project prior to altitude exposure for personal reasons unrelated to the conditions of the overall project and its component studies. Of the 47 individuals who completed both sea-level and altitude testing during the three-year project, 39 either were not taking study-related medications or were placebo-treated and were included in the current analysis.

Volunteer test subjects were healthy, non-smoking, young-adult women recruited from student-aged populations around Palo Alto, CA (1996, 1998) and from student-aged populations around Natick, MA, and active duty military personnel stationed at Soldier Systems Command, Natick, MA (1997). The mean (±SD) age, height and weight of the volunteers was 23.3±4.1 yrs (range 18-33 yrs; 95%CI, 22.0 to 24.5 yrs), 167.4±6.5 cm (range 154-183 cm; 95%CI, 165.3 to 169.5 cm) and 67.7±10.4 kg (range 42-94 kg; 95%CI, 64.3 to 71.1 kg), respectively. All volunteers had a history of regular menstrual cycles of 28-36 days in length and had not been treated with oral contraceptive or other hormonal therapy or been pregnant in the six months immediately preceding their participation in the study. All were born and raised at altitudes less than 1500 m and had resided at sea level for a minimum of 6 months immediately preceding their participation in the study. None had any contraindication to altitude exposure or to any of the testing procedures included in the overall project as adjudged from information obtained by a directed medical history, physical examination, and specific clinical laboratory screening tests. They had hemoglobin values within the normal range for their age and adequate iron stores as indicated by serum ferritin levels within the normal range for their age. Most were in moderate to very good physical condition with a mean maximal oxygen uptake (VO_2max) of 38.1±7.8 $ml \cdot kg^{-1} \cdot min^{-1}$ (range 17.4-53.9 $ml \cdot kg^{-1} \cdot min^{-1}$; 95%CI, 35.6 to 40.7 $ml \cdot kg^{-1} \cdot min^{-1}$).

Prior to her participation, each volunteer test subject was briefed on all aspects of the study including the potential risks involved. Each was made aware of her right to withdraw from the studies at any time without prejudice. After appropriate consideration of the information presented about the study, each subject gave verbal and written consent to her voluntary participation. Study investigators adhered to US Army Regulation 70-25 and US Army Research and Materiel Command Regulation 70-25 on the use of human volunteers in research.

MENSTRUAL CYCLE PHASE

Initially volunteer subjects were randomly assigned in equal numbers to be exposed to sea level followed by high altitude during either the follicular or the luteal phase of their

menstrual cycles. The studies in 1996 and 1998 were designed to test the individual volunteer subjects in the same phase of different menstrual cycles, and altitude exposures were initiated at the beginning of each individual's assigned menstrual cycle phase. In 1997, the volunteers were tested at sea level followed by high-altitude testing during the same phase of a single menstrual cycle, and the sea-level and altitude exposure was initiated within 7 days of the beginning of each individual's assigned menstrual cycle phase.

For the purpose of initiating sea-level or altitude exposure in the assigned menstrual cycle phase, the follicular and luteal phases were tentatively identified by the volunteer subject reporting the onset of her menstrual bleeding and her detection of the rapid increase of lutenizing hormone ("LH surge") in her urine associated with ovulation and detected in the first morning urine using a commercially available ovulation detection kit (OvuQuick, Becton-Dickinson, Rutherford, NJ or First Response, Carter Wallace Products, New York, NY). The beginning of the follicular phase was defined by the onset of menstrual bleeding, and the time between the initiation of menstrual bleeding and detection of the LH surge was designated to be the follicular phase. The luteal phase was defined as beginning the day following detection of the LH surge and lasting until the onset of menstrual bleeding. Documentation of the actual menstrual cycle phase was based upon measured levels of estradiol and progesterone in serum samples taken at specified intervals during sea-level or altitude exposure and analyzed after each study was completed. In 1996 and 1998 samples were obtained on days 3,6,9,10, and 12 of the sea-level and altitude exposures, which corresponded to the same day of their putative cycle phase. In 1997, samples were obtained on the fourth day of the sea-level exposure and on both days of the subsequent altitude exposure (study days 7 and 8).

Serum levels of estradiol and progesterone were measured in duplicate using either radioimmunoassay (RIA;1996; Coat-A-Count, Diagnostic Products, Los Angeles, CA) or chemiluminescent enzyme immunoassay (1997, 1998; Immunolite, Diagnostic Products Corp., Los Angeles, CA). All samples for one subject were analyzed together to avoid inter-assay variations. For the RIA, intra-assay variances were 6.0% and 7.6% for estradiol and progesterone, respectively, and the inter-assay variances were 9.6% and 11.9%. The intra-assay variances for the chemiluminescent immunoassays were 9.5% for estradiol and 7.9% for progesterone, and the inter-assay variances were 16.0% and 10% respectively. We accepted estradiol values of 10-200 pg•ml and progesterone values of 0.1-1.5 ng•ml as being indicative of the follicular phase, and values of 50-115 pg•ml and 2.5-28 ng•ml, respectively, as being indicative of the luteal phase.

ALTITUDE EXPOSURE

Due to the requirements of the overall project, of which this investigation was only a part, two different scenarios were used to create the combination of sea-level and altitude exposure during each of the three years of study. In 1996 and 1998, sea-level testing took place in the Geriatric Research and Education Center of the Palo Alto

Veterans Affairs Health Care System, Palo Alto, CA (15 m; P_B=758 mmHg, range 748-762 mmHg). One to three months after completing sea-level testing, volunteer subjects were flown in commercial airplanes to Colorado Springs, CO (1850 m), then driven in automobiles to the US Army High Altitude Research Laboratory Facility on the summit of Pikes Peak, CO (4300 m; P_B=462 mmHg, range 458-464 mmHg) over a period of 2 to 5 hours. For each individual, travel to the Pikes Peak laboratory began on the second day of her assigned cycle phase. Each volunteer subject remained on the summit continuously for 12 days, during which time the same observations and testing schedule that had been accomplished at sea level was repeated. Temperature in the laboratory during altitude exposure was maintained between 19 and 23 °C and relative humidity fluctuated between 10 and 40 %. During the studies in Palo Alto and on Pikes Peak the volunteers consumed a controlled diet designed to minimize body-weight change and eliminate consumption of caffeine (see Mawson et al., 2000 for details of the diet). The volunteer subjects were requested to maintain their normal exercise activity level throughout the study.

In 1997, both sea-level and altitude exposure took place in a hypobaric chamber at the US Army Research Institute of Environmental Medicine, Natick, MA (50 m; P_B=756 mmHg, range 738-762 mmHg) during a period of six consecutive days. The exposures were timed to take place during each volunteer's assigned phase of a single menstrual cycle. Sea-level observations and testing were done at ambient barometric pressure. Following sea-level testing, the chamber was decompressed at a rate of 45 mmHg/min to a pressure of 446 mmHg (approximately equivalent to 4300 m altitude). The volunteer subjects remained in the chamber at 446±2 mmHg continuously for 52 hours while the same testing and observation schedule that was accomplished at sea level was repeated. Ambient temperature and relative humidity in the chamber were maintained at 19±2 °C and 40±5 % respectively throughout the exposure. As in 1996 and 1998, volunteer subjects consumed a controlled, balanced diet designed to minimize body weight loss. Because of the confinement in the hypobaric chamber, volunteer subjects were limited to relatively sedentary activities during the study.

Although the use of two different sea-level/altitude exposure scenarios was a constraint imposed by the overall project, the consistent altitude in both scenarios allows the data to be combined to test both hypotheses. The data on incidence of AMS from the 1997 and first 52 hours of 1996 and 1998 address the question of whether women in the luteal phase are preacclimatized to altitude by virtue of progesterone stimulation of their ventilation. The data on the time course of AMS symptoms from 1996 and 1998 address the question of whether women in the luteal phase of their cycle acclimatize faster then women in the follicular phase.

ASSESSMENT OF AMS

Symptoms of AMS were assessed multiple times at sea level using the Environmental Symptoms Questionnaire (ESQ). They were assessed twice daily during the high altitude exposures using the ESQ and the Lake Louise AMS Scoring System

(LLS). The ESQ is a self-administered, 68-question inventory of symptoms induced by high altitude exposure and other stressful environments (Sampson et al., 1983) that has been well validated and widely used for documenting AMS in mountain environments and hypobaric chambers (Sampson et al., 1994). Symptom severity is self-rated on a scale of 0 to 5, with a score of "0" indicating the absence of symptoms and "5" representing the symptom present at maximum intensity (Sampson et al., 1983). Weighted averages of scores on specific groups of symptoms considered to represent primarily cerebral manifestations of AMS (e.g., headache, lightheaded, dizzy) designated "AMS-C," or respiratory manifestations (e.g., short-of-breath, hurts-to-breathe) designated "AMS-R" were calculated for each subject for each assessment. Acute mountain sickness was judged to be present if an individual's AMS-C score was ≥0.7 or their AMS-R score was ≥0.6 (Sampson et al., 1983). Additionally, a "severity index" value was assigned to each AMS-C and AMS-R scores for each individual. The severity index is based upon the increments in standard deviation from the mean scores for the 58 men reported by Sampson et al. (1983).

The LLS consists of a self-reported assessment of five AMS symptoms using a scale of 0 to 3 and an investigator-conducted objective assessment of three "clinical" signs of AMS (i.e., mental status changes, presence of ataxia and peripheral edema) using scales of 0 to 4 (mental status and ataxia) and 0 to 2 (peripheral edema; Roach et al., 1993). For the self-reported assessment, "0" indicates the absence of that symptom and "3" the most severe experience of the symptom. Likewise, for the clinical signs "0" indicates the lack of the sign, while "4" and "2" represent the sign in its most severe manifestation. The sum of the self and clinical assessment scores was calculated (Roach et al., 1993) for each subject for each assessment.

Two separate criterion scores were used to judge the presence of AMS detected by the LLS. Using the originally proposed criteria, AMS was judged to be present if an individual had a headache (i.e., score of ≥1 on the headache question) and a total score of ≥3 on the combined self and clinical assessment after having been exposed to altitude for more than two hours (Roach et al., 1993). Additionally, because Maggiorini and co-workers (1998) have reported that a total LLS score of ≥5 on the combined self- and clinical assessment, irrespective of the presence of headache, may be most predictive of "clinically apparent" AMS at altitudes between 2850 and 4559 m, we also evaluated the LLS scores using those criteria. The LLS scoring system has been demonstrated to reliably detect the presence of AMS in mountain environments (Maggiorini et al., 1998; Savourey et al., 1997) and in hypobaric chambers (Savourey et al., 1995, 1997), and to correlate with ESQ scores (Savourey et al., 1995; Maggiorini et al., 1998).

Incidence of AMS was defined as the number of previously asymptomatic test volunteers in a group who achieved or exceeded the criterion score value on a measure of AMS for the first time during the each 24 hr period divided by the total number of volunteer subjects exposed to altitude in that group. The prevalence of AMS was defined as the number of test volunteers in a group who achieved or exceeded the criterion score

value on a measure of AMS during each 24-hour period divided by the total number of volunteer subjects in that group who were present at altitude during that period of time.

RESTING VENTILATORY MEASUREMENTS

Ventilatory acclimatization was assessed by measuring each volunteer subject's resting minute ventilation ($\dot{V}_{E\,(rest)}$), end-tidal CO_2 ($P_{ET}CO_2$), blood oxygen saturation (SpO_2) and heart rate (HR) during rest at sea level and high altitude. All measurements were made with the volunteer subject in a comfortable, seated position while breathing through a low resistance respiratory valve and breathing circuit. The $\dot{V}_{E\,(rest)}$ and $P_{ET}CO_2$ measurements were made using a computer-controlled, open-circuit spirometry and gas analyzer system (Vmax299, SensorMedics Corp., Yorba Linda, CA). Blood oxygen saturation and HR were made simultaneously by a finger pulse oximeter (N-200, Nellcor Inc., Pleasanton, CA). Except for the initial altitude measures (Day 1) in 1997 and 1998 (see below), the resting measurements were made in the morning prior to eating and at approximately the same time for each individual. Before beginning data collection, volunteer subjects were given several minutes to adjust to the seated position and breathing circuit, then a minimum of ten minutes of resting ventilation, SpO_2 and HR data were collected. Resting measurements were made at sea level on days 1 and 7 (1996) or 2 and 8 (1998), and on days 2,3,5,7,12 (1996) and 1,2,3,5,7,9,12 (1998) at high altitude. In 1997 resting measurements were made on days 1 and 3 at sea level and days 1,2,3 at high altitude. During 1997 and 1998, the initial measurements (Day 1) were made approximately two hours after the volunteer subjects reached 4300 m, which was during the afternoon. In addition to the resting measurements, SpO_2 and HR measures were made with the volunteer subjects in a supine position immediately upon awakening in the morning using a finger pulse oximeter (N-200, Nellcor Inc., Pleasanton, CA; Oxyshuttle, SensorMedics Corp, Yorba Linda, CA). These measurements were made in conjunction with the collection of expired air for calculation of basal metabolic rates (Mawson et al., 2000), and were done daily.

STATISTICAL METHODS

Because the assessment of AMS was a sub-study of the larger project, the sample sizes for each study year were based upon statistical power estimations for the dependent variables of interest to the objectives of the overall study, rather than upon measures of AMS. However, the sample size of 23 individuals in the follicular phase and 16 individuals in the luteal phase groups that was achieved over the three year period of the study was determined to provide at least an 80% chance of detecting a difference of 35% in incidence of AMS between the luteal and follicular phases using a sign test with a significance level of α=0.05 (Cohen, 1977). Thirty-five percent difference in incidence reflects the minimal change previously reported for the successful prevention of AMS by staged ascent and pharmacological prophylaxis with acetazolamide at 4300 m altitude (Evans et al., 1976; Forwand et al., 1968; Stamper et al., 1980).

All values in text and tables are presented as mean±standard deviation (SD). Additionally, the 95% confidence interval (95% CI) for the mean is presented. Standard error of the mean (SEM) is used in the figures to enhance the visual clarity.

The calculated symptom scores from the ESQ and LLS were evaluated for statistically significant differences using a two-way (menstrual cycle, time at altitude) analysis of variance (ANOVA), with repeated measures or, when the criteria for parametric testing was not present, using Wilcoxan rank-sum (Mann-Whitney-U) tests. Significant main effects over time at altitude and interactions between time at altitude and menstrual cycle phase detected using ANOVA were localized within conditions using a Tukey's test. The ANOVA and post hoc localization testing was performed using a computerized statistical package (SigmaStat 2.0, Jandel Scientific Software, San Rafael, CA). Incidence of AMS was evaluated for difference between follicular and luteal groups using t-tests. The difference in prevalence and severity scores was evaluated using non-parametric binomial sign tests for dependent samples. Correlation analysis was performed using the SigmaStat computerized statistical package.

RESULTS

MENSTRUAL CYCLE PHASE AND OVARIAN HORMONES

Within the experimental design of this study, menstrual cycle phase is an independent variable. As a practical matter, the control over this variable proved problematic, at best. Although each volunteer test subject was assigned to be exposed to high altitude in a specific menstrual-cycle phase such that there would be equal numbers of individuals in the follicular and luteal phase groups, *post hoc* analysis of the serum estradiol and progesterone sampled during the altitude exposures revealed hormone levels in some individuals that were inconsistent with their assigned cycle-phase. As a consequence, volunteers either were reassigned to the opposite cycle-phase group for statistical analysis (if appropriate) or dropped from the analysis of cycle-phase effects. This resulted in unequal sample sizes between follicular- and luteal-phase groups, especially during the 12-day altitude exposure when very few volunteers assigned to the luteal phase remained in that phase throughout the entire exposure. Additional differences in sample size resulted from missed blood collections and laboratory mishaps.

Based upon *post hoc* analysis of blood hormone levels, three volunteers who were originally assigned to be in the luteal cycle-phase during high-altitude exposure were found instead to have hormone levels consistent with the follicular phase. Whether this was due to failure to accurately predict the cycle phase or to these individuals experiencing an aborted luteal phase cannot be determined from the existing data. Because the hormone levels in these three individuals were consistent with follicular phase throughout altitude testing, they were included in the follicular-phase group for cycle-phase analysis. Six other volunteers had persistently low estradiol levels consistent with abnormal, very likely anovulatory menstrual cycles during high-altitude exposure. Because

the hypothesis of this study was that putative cycle-phase differences in AMS are the result of differences in cycle-phase related ovarian-hormone levels, and because low ovarian-hormone levels are consistent with early follicular phase, these individuals with low estradiol levels were included in the follicular phase group for analysis of cycle-phase effects.

In addition to the volunteer subjects who were exposed to high altitude in opposite menstrual-cycle phase to which they were originally assigned and those with low estradiol, some individuals during the 1996 and 1998 studies changed cycle phase during the 12 days of altitude exposure. Two individuals who started the altitude exposure in the follicular phase had serum ovarian-hormone levels consistent with the luteal phase by the end of the exposure. Six other individuals, who arrived at Pikes Peak in the luteal phase, experienced menstruation during their 12-day sojourn at altitude and had serum ovarian-hormone levels consistent with the follicular phase by the end of the altitude exposure. With all eight individuals, the apparent change in phase occurred after the first 60 hrs of altitude exposure. Consequently, for statistical analysis of cycle phase effects, these individuals were considered as being in the phase in which they arrived at Pikes Peak (i.e., 6 luteal, 2 follicular) for the first 60 hrs of altitude exposure and were dropped from analysis after they changed cycle phase. Thus, based upon the serum ovarian hormone levels, 24 women volunteers were exposed to high altitude for at least the initial 60 hrs in the follicular phase of their menstrual cycle, and 15 in their luteal phase. During the 12-day altitude exposure, 15 women were determined to be in the follicular phase of their cycle throughout the exposure, but only 3 were in the luteal phase.

As a consequence of the specific ovarian hormone levels designated as criteria to define the menstrual-cycle phases, the serum levels of estradiol and progesterone of the volunteer subjects, when grouped by menstrual cycle phase (Tables 1 and 2), were, by definition, consistent with 'normal' values for the follicular and luteal cycle-phases in menstruating women of this age group (Landgren et al., 1980). Overall there was conspicuous intra- and inter-individual variation in the serum levels of the ovarian hormones, however. Such variation is characteristic of women in this age and may reflect inhibitory influences of various stress factors acting through the hypothalamic-pituitary-gonadal axis and/or the normal prolonged maturation process of the ovary (Vuorento et al., 1989).

Mean serum estradiol and progesterone levels measured on the third day of altitude exposure (i.e., the approximate time of greatest AMS prevalence and severity) and the calculated area-under-the-curve (AUC) of the measured serum levels over time during the first three days of sea-level and altitude exposure are presented in Table 1. (AUC serves as an integrated estimate over time of potential tissue exposure to circulating hormones.)

On day 3 of altitude exposure, there were statistically significant differences between cycle-phase groups for both estradiol (29.0 pg/ml, CI = 2.2 to 55.8 pg/ml, $p=0.035$) and progesterone levels (5.0 ng/ml, CI = 2.8 to 7.2 ng/ml, $p=<0.001$) with the

mean values higher in the luteal phase. Likewise, the AUC values for these hormones were also higher during the luteal phase, and the difference was statistically significant (estradiol = 78.4, CI = 46.0 to 110.8, p=<0.001; progesterone = 3.9, CI = 6.0 to 18.5, p=<0.001). There were no statistically significant differences between mean AUC values for the first three days at sea level and at high altitude.

Table 1. Mean Serum Ovarian Hormone Values at Sea Level and During Initial 60-Hours Exposure to 4300 m Altitude*

MENSTRUAL-CYCLE PHASE	ESTRADIOL, pg/ml (95% CI)			PROGESTERONE, ng/ml (95% CI)		
	Day 3 Altitude	Area Under Curve [AUC]		Day 3 Altitude	Area Under Curve [AUC]	
		Sea Level	Altitude		Sea Level	Altitude
Follicular	62.3 (44.1 to 80.5) n=22	90.6 (67.9 to 113.3) n=23	117.7 (82.5 to 152.9) n=24	0.9 (0.7 to 1.1) n=22	2.8 (1.4 to 4.2) n=22	2.0 (1.5 to 2.5) n=24
Luteal	91.3 (70.8 to 111.8) n=15	181.4 (141.6 to 221.2) n=15	184.5 (150.1 to 218.9) n=15	5.9 (3.1 to 8.7) n=15	10.6 (6.4 to 14.8) n=15	11.6 (6.5 to 16.7) n=15

"CI" indicates 95% confidence interval; "n" indicates sample size.
*Volunteer subjects were initially allocated to menstrual-cycle phase groups in equal numbers based upon predicted cycle phase. Final assignment was based upon *post hoc* analysis of hormone levels in blood samples collected during the sea-level and altitude exposures. Differences in group size reflect both inaccurate prediction of menstrual cycle phase and the inherent instability of the luteal phase. Within group differences are the result of missing samples.

Just as the hormone exposure over the first three days of altitude exposure was different between menstrual-cycle phases, the same was true for the 12-day exposure. Again, this was expected due to the grouping on the basis of criterion hormone levels. The mean AUC values for estradiol and progesterone during the 12-day exposure at sea level and altitude (1996 or 1998) in the individuals who remained in the same cycle phase throughout the exposure are presented in Table 2.

Both estradiol and progesterone AUC were significantly lower during the follicular phase (estradiol = 378.0 pg/ml, 95% CI = 611.3 to 146.7 ng/ml, p=0.002; progesterone = 74.0 pg/ml, 95% CI = 82.6 to 65.3 pg/ml, p=<0.001). Interestingly, there was a suggestion of a suppressive effect of altitude exposure on progesterone with the mean AUC for the 12-day exposure lower at high altitude. Statistically, the overall altitude effect on progesterone was significant (p=0.049), with no statistically significant interaction between altitude and cycle phase (p=0.127). However, the mean difference (71.3 pg/ml, 95% CI = -507.7 to 650.2 pg/ml) was not statistically significant (p=0.789).

Table 2. Mean ovarian Hormone Levels at Sea Level and During 12-Day Exposure to 4300 m Altitude*

DAY	ESTRADIOL, pg/ml (95% CI)				PROGESTERONE, ng/ml (95% CI)			
	Sea Level		Altitude		Sea Level		Altitude	
	Follicular	Luteal	Follicular	Luteal	Follicular	Luteal	Follicular	Luteal
1	27.7 (2.0 to 53.3) n=4	76.6 (39.9 to 113.2) n=4	57.2 (37.2 to 77.2) n=12	105.9 (79.4 to 132.4) n=10	1.0 (0.2 to 1.8) n=4	5.7 (1.2 to 10.1) n=4	1.3 (1.0 to 1.6) n=10	9.0 (4.8 to 13.0) n=10
3	41.9 (22.2 to 59.6) n=15	94.5 (74.6 to 114.3) n=11	63.9 (46.3 to 81.6) n=23	90.7 (68.6 to 112.8) n=14	1.0 (0.6 to 1.4) n=18	6.7 (4.8 to 8.6) n=15	0.9 (0.6 to 1.0) n=21	6.2 (3.3 to 9.1) n=14
6	49.7 (36.4 to 62.9) n=19	103.9 (78.7 to 129.1) n=10	85.4 (35.4 to 135.5) n=15	106.7 (67.6 to 145.7) n=6	1.0 (0.7 to 1.2) n=13	8.5 (5.2 to 11.9) n=11	0.7 (0.6 to 0.8) n=14	7.6 (2.3 to 12.8) n=7
9	64.9 (20.7 to 109.1) n=6	106.3 (61.2 to 151.5) n=3	66.5 (34.5 to 98.5) n=13	105.8 (49.9 to 161.7) n=3	0.6 (0.3 to 0.9) n=6	11.5 (-1.8 to 24.8) n=3	0.7 (0.5 to 0.8) n=13	7.2 (-0.4 to 14.8) n=5
10	76.4 (34.7 to 118.0) n=10	83.7 NA n=1	70.7 (44.8 to 96.6) n=9	100.1 (42.7 to 157.5) n=3	0.78 (0.4 to1.2) n=10	9.8 NA n=1	0.7 (0.4 to 1.1) n=9	9.2 (-0.8 to 19.2) n=4
12	60.4 (33.7 to 87.1) n=13	81.1 (-388.4 to 550.5) n=2	48.0 (26.1 to 69.9) n=6	77.1 (-494.1 to 648.2) n=2	1.0 (0.5 to 1.4) n=13	8.5 (-60.4 to 77.5) n=2	0.6 (0.4 to 0.7) n=6	4.0 (-5.8 to 13.8) n=3
	Area Under Curve [AUC]							
1-12	554.2 (429.2 to 679.2) n=14	934.9 (457.0 to 1412.8) n=3	500.7 (357.0 to 644.1) n=15	801.7 (308.8 to 1294.6) n=3	9.9 (5.2 to 14.6) n=14	85.8 (16.2 to 155.4) n=3	6.8 (5.4 to 8.2) n=15	76.5 (29.3 to 123.7) n=3

"CI" indicates 95% confidence interval for the mean; "n" is the sample size; "NA" stands for "not applicable".
*Volunteer subjects were initially allocated to menstrual-cycle phase groups in equal numbers based upon predicted cycle phase. Final assignment was based upon *post hoc* analysis of hormone levels in blood samples collected during the sea-level and altitude exposures. Differences in group size reflect both inaccurate prediction of menstrual cycle phase and the inherent instability of the luteal phase. Within group differences are the result of missing samples.

Finally, although the hypothesis that the study was designed to test was that the different hormone levels associated with menstrual cycle phases, especially progesterone, would affect altitude acclimatization, the high intra- and inter-individual variability in hormone levels documented in the volunteer subjects raised the question of whether ovarian hormone levels might effect acclimatization independently of cycle phase. To allow

exploration of that possibility, ovarian hormone blood levels and the AUC on the 12th day of exposure were tabulated for all volunteer subjects without regard to menstrual-cycle phase (Table 3). When the hormone and AUC values were combined without regard to menstrual cycle phase, the result resembled a random cross section of cycle phases, for there were no statistically significant effects of altitude or day of exposure on the mean hormone or AUC values.

Table 3. Mean Ovarian Hormone Levels for All Subjects at Sea Level and During 12-Day Exposure to 4300 m Altitude*

DAY	ESTRADIOL, pg/ml (95% CI)		PROGESTERONE, ng/ml (95% CI)	
	Sea Level	Altitude	Sea Level	Altitude
1	52.1 (25.4 to 78.8) n=8	79.3 (61.0 to 97.8) n=22	3.4 (0.8 to 6.0) n=8	4.8 (2.4 to 7.2) n=22
3	64.1 (47.8 to 80.4) n=26	74.0 (60.2 to 87.8) n=37	3.6 (2.3 to 4.9) n=26	2.9 (1.6 to 4.2) n=37
6	61.6 (31.6 to 91.6) n=9	91.5 (55.8 to 127.2) n=21	4.1 (0.1 to 8.1) n=9	3.0 (0.9 to 5.1) n=21
9	78.7 (47.8 to 109.6) n=9	73.9 (46.9 to 100.9) n=16	4.2 (-0.5 to 8.9) n=9	2.5 (0.4 to 4.6) n=18
10	77.0 (39.9 to 114.1) n=11	78.1 (57.0 to 99.2) n=12	1.6 (-0.2 to 3.4) n=11	3.2 (0.31 to 6.1) n=14
12	63.2 (38.5 to 87.5) n=15	55.3 (28.0 to 82.6) n=8	2.0 (0.1 to 3.9) n=15	1.7 (-0.3 to 3.7) n=9
	Area Under Curve [AUC]			
1-12	591.8 (463.1 to 720.5) n=25	593.4 (439.9 to 746.9) n=23	29.2 (14.9 to 43.5) n=22	23.4 (14.9 to 41.9) n=21

"CI" indicates 95% confidence interval; "n" is the sample size.
*Differences in sample size due to volunteer subjects in 1997 exposed to altitude for only 60 hours, attrition out of initial menstrual cycle phase by a few individuals, and missing samples.

RESTING VENTILATION AND OXYGEN SATURATION

As expected, exposure to 4300 m altitude caused an increase in resting ventilation ($\dot{V}_{E\,(rest)}$) measured directly and as evidenced by a decrease in partial pressure of carbon

dioxide in end-tidal expired breath samples (P_{ET} CO_2). Changes in both parameters were apparent after the first few hours of altitude exposure (Table 4).

Table 4. Mean Resting Ventilation and End-tidal Carbon Dioxide at Sea Level and During First 60-Hours Exposure to 4300 m Altitude

Menstrual-cycle Phase	Sea Level [mean]	Altitude		
		Day 1 pm	Day 2 am	Day 3 am
	Resting Ventilation, l/min (95% CI)			
Follicular	8.2 (7.5 to 9.0) n=23	9.7 (8.9 to 10.5) n=23	10.1 (9.4 to 10.9) n=21	10.7 (9.6 to 11.5) n=19
Luteal	9.1 (8.1 to 10.1) n=16	10.8 (9.0 to 12.5) n=16	10.9 (9.3 to 12.4) n=15	10.7 (9.3 to 12.1) n=15
	Resting End-tidal CO_2, mmHg (95% CI)			
Follicular	38.4 (37.3 to 39.5) n=23	34.5 (33.2 to 35.7) n=23	32.1 (30.5 to 33.8) n=21	29.9 (27.7 to 32.1) n=19
Luteal	37.7 (36.3 to 39.0) n=16	33.9 (31.4 to 36.4) n=16	31.2 (29.2 to 33.2) n=15	29.4 (27.7 to 31.1) n=15

"CI" indicates 95% confidence interval for the mean; "n" is the sample size.
Sea-level values are derived from individual means of at least two measurements made on different days.

After 60 h of altitude exposure, $\dot{V}_{E\,(rest)}$ was increased to a mean of 129.1 % (95% CI = 116.6 to 141.5 %) and 118.5 % (95% CI = 110.0 to 127.0 %) of sea-level values in the follicular and luteal groups, respectively. There was no statistically significant effect of cycle phase (10.6 %, 95% CI = -4.8 to 26.0 %, p=0.172) or altitude exposure (6.3 %, 95% CI = -17.3 to 4.6 %, p=0.250). In parallel with the increase in $\dot{V}_{E\,(rest)}$, $P_{ET}CO_2$ was decreased to a mean of 78.7 % (95% CI = 73.9 to 83.5 %) lower than the sea-level value in the follicular group and 77.8 % (95% CI = 74.6 to 80.9 %) in the luteal group, a statistically insignificant difference (0.9 mmHg, 95% CI = -5.0 to 6.8, p=0.757). The decrease in $P_{ET}CO_2$ over the first 60 h at high altitude expressed as percent sea-level value was statistically significant (11.6 %, 95% CI = 0.8 to 15.4 %, p=<0.001), however.

Resting ventilation continued to increase and $P_{ET}CO_2$ to decrease throughout the entire 12 days of altitude exposure at Pikes Peak in 1996 and 1998 consistent with progressive ventilatory acclimatization of the volunteer subjects (Table 5). Resting ventilation increased to mean values of 119.4 % (95% CI = 103.2 to 135.7 %) and 106.0 %

(95% CI = 92.8 to 119.1 %) of the sea-level values on the afternoon of the day of ascent in the follicular and luteal groups respectively and to 142.3 % (95% CI = 114.1 to 170.6 %) and 124.7 % (95% CI = 97.4 to 151.9 %) of the sea-level values on the morning of the 12th day of altitude exposure. The increase in resting ventilation over time at altitude expressed as percent of sea-level values was statistically significant (24.1 %, 1.9 to 46.3 %, p=0.034), but the differences between luteal and follicular groups were not (p=0.927). The increase in ventilation at altitude resulted in a decrease in $P_{ET}CO_2$ from 91.0 % (95% CI = 88.1 to 94.0 %) and 93.6 % (95% CI = 81.9 to 105.2 %) of the sea-level values on the afternoon of the day of ascent in the follicular and luteal groups respectively and to 73.4 % (95% CI = 70.5 to 76.3 %) and 72.8 % (95% CI = 63.4 to 82.2 %) of the sea-level values on the morning of the 12th day of altitude. The decrease in $P_{ET}CO_2$ from the first to the 12th day of altitude exposure expressed as percent of sea-level values was statistically significant (18.6 %, 95% CI = 13.8 to 23.5 %, p=<0.001), but the difference between menstrual cycle phase groups was not (p=0.943).

Table 5. Mean Resting Ventilation and End-tidal Carbon Dioxide at Sea Level and During 12-Day Exposure to 4300 m Altitude

Day	Resting Ventilation, l/min (95% CI)		Resting End-tidal CO_2, mmHg (95% CI)	
	Follicular	Luteal	Follicular	Luteal
Sea Level [mean]	7.9 (6.9 to 8.9) n=16	8.3 (7.1 to 9.5) n=8	38.5 (37.2 to 39.9) n=16	38.7 (36.9 to 40.4) n=8
1	9.0 (8.2 to 9.9) n=16	8.8 (7.0 to 10.7) n=8	35.0 (34.0 to 36.1) n=16	36.2 (31.6 to 40.8) n=8
2	9.8 (9.0 to 10.7) n=16	9.1 (7.7 to 10.5) n=7	33.2 (31.8 to 34.7) n=16	34.2 (32.6 to 35.8) n=7
3	9.8 (8.8 to 10.8) n=14	9.3 (8.0 to 10.7) n=7	31.7 (29.9 to 33.6) n=14	31.9 (30.7 to 33.1) n=7
5	10.9 (10.0 to 11.9) n=16	11.0 (9.7 to 12.4) n=6	30.3 (28.6 to 31.9) n=15	31.4 (29.0 to 33.8) n=6
7	10.6 (9.5 to 11.7) n=14	10.2 (5.7 to 14.6) n=3	29.8 (28.4 to 31.2) n=16	28.8 (24.7 to 32.9) n=3
9	10.0 (8.8 to 11.2) n=4	7.9 NA n=1	29.3 (25.2 to 33.4) n=5	29.3 NA n=1
12	10.7 (9.1 to 12.3) n=13	11.1 (3.1 to 19.2) n=3	28.2 (27.0 to 29.5) n=16	26.6 (25.3 to 28.0) n=3

"CI" indicates 95% confidence interval for the mean; "n" is the sample size.
Sea-level values are derived from individual means of at least two measurements made on different days.
Differences in sample size are due to volunteer subjects in 1997 exposed to altitude for only 60 hours, attrition out of initial menstrual cycle phase by some individuals, and missing samples.

Initial exposure to 4300 m altitude resulted in a drop in percent oxygen saturation of the blood (SaO_2) measured by pulse oximetry at rest during the first 60 hr of exposure (Table 6) in the hypobaric chamber and at Pikes Peak. The greatest decrease was on the first day at altitude (-17.6 %, 95% CI = -15.8 to -19.5 %, p=<0.001). The SaO_2 rose progressively from the 1st thru the 3rd day of altitude exposure (2.8 %, 95% CI = 0.1 to 5.4, p=0.040), but the values during all three days at altitude were statistically significantly different from the sea-level mean value (p=<0.001). There were no statistically significant differences between the values for the follicular and luteal groups at sea level or during the first 60 hours of altitude exposure (p=0.490).

Table 6. Mean Resting Percent Oxygen Saturation of Blood at Sea Level and During First 60-hours Exposure to 4300 m Altitude

Menstrual-cycle Phase	Sea Level (95% CI)	Altitude (95% CI)		
		Day 1 pm	Day 2 am	Day 3 am
Follicular	98.0 (97.6 to 98.4) n=22	79.0 (76.6 to 81.3) n=22	82.6 (79.6 to 85.5) n=20	83.8 (80.5 to 90.7) n=19
Luteal	98.0 (97.5 to 98.5) n=16	82.3 (79.4 to 85.2) n=16	83.3 (81.4 to 85.2) n=16	82.3 (80.2 to 84.5) n=16

"CI" indicates 95% confidence interval; "n" is the sample size.
Percent oxygen saturation measured at rest by pulse-oximetry; sea-level values are derived from individual means of at least two measurements made on different days. Differences in group size reflects inaccurate prediction of menstrual cycle phase. Differences in sample size within the follicular phase group was due to voluntary discontinuation of altitude exposure by test subjects.

Due to the increase in ventilation caused by ongoing acclimatization, the SaO_2 at rest and upon first awakening in the morning rose progressively during the 12 days of altitude exposure at Pikes Peak (Table 7). The rise in SaO_2 was statistically significant both at rest (8.7 %, 95% CI = 6.0 to 11.5 %, p=<0.001) and upon awakening (2.4 %, 95% CI = 0.3 to 4.5 %, p=0.029), but the menstrual cycle phase differences were not statistically significant (p=0.126 and p=0.631, 'at rest' and 'on awakening,' respectively).

ACUTE MOUNTAIN SICKNESS

The overall pattern of AMS symptoms manifested by the women volunteers was similar to the pattern seen most often in the many men and in the few women previously studied at Pikes Peak and in the hypobaric chamber, i.e., symptoms were most frequent and severe early in the altitude exposure and decreased or resolved completely with continued exposure. This pattern was readily apparent in data from both the ESQ and the LLS symptom-score instruments. Unlike the obvious temporal pattern, few clear-cut

Initial Sixty Hours of Altitude Exposure

The first three days of altitude exposure were characterized by rapid onset of AMS followed by some initial resolution of symptoms. The onset and resolution were seen in both collective symptom scores and in the number of individuals identified as having AMS based upon their individual scores. There was a great deal of variability between individuals, and many volunteers continued to qualify as having AMS long after the mean scores for the group had dropped below criterion scores (Figure 1)

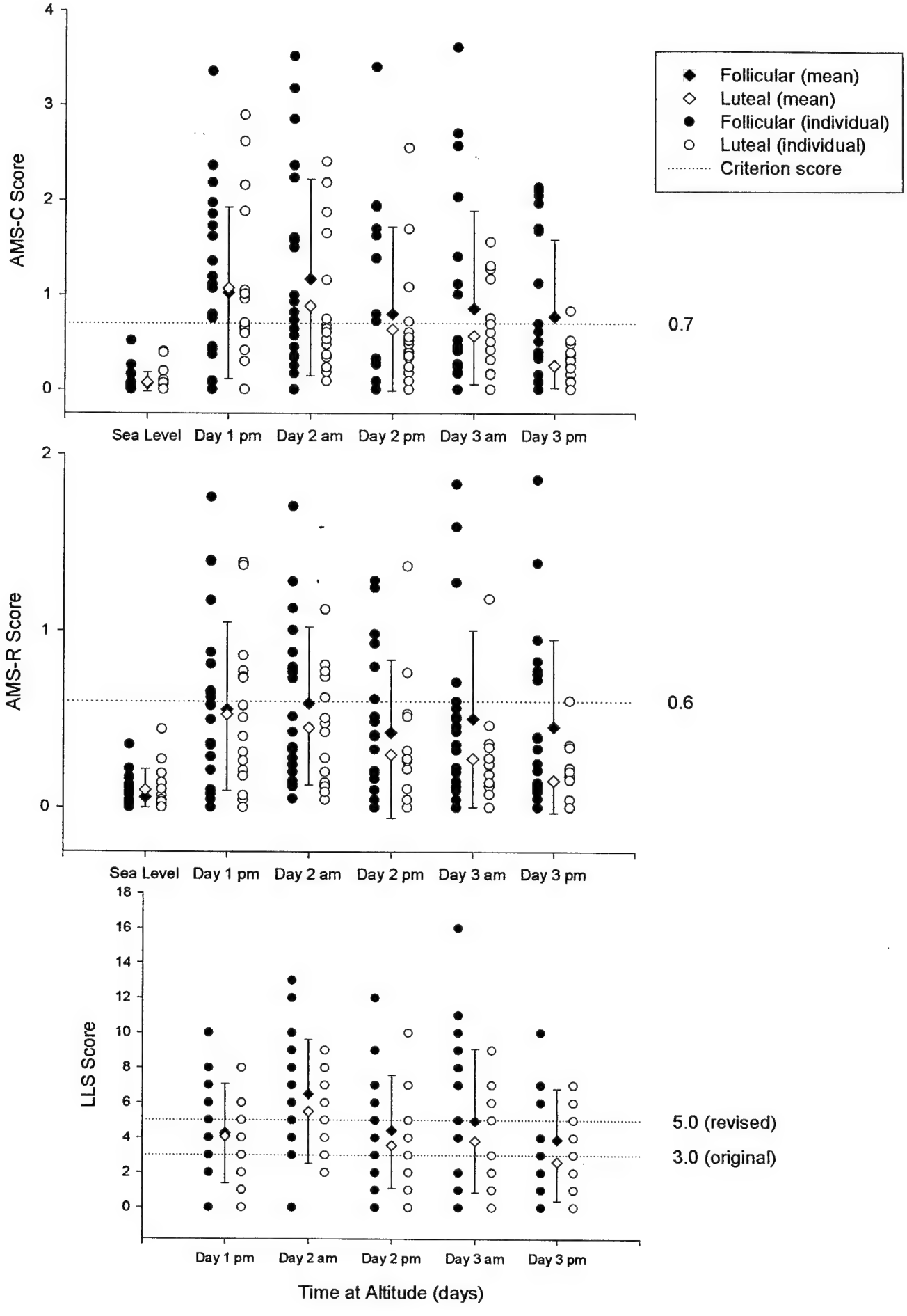
Mean symptom score values peaked on the morning of the second day of exposure and then decreased more-or-less progressively after that time (Figure 3). The overall effect of altitude on AMS-C, AMS-R and LLS scores was statistically significant ($p=<0.001$). The greatest difference in ESQ scores was between sea level and the morning of the second day of altitude exposure (AMS-C mean difference 0.97, 95% CI = 0.65 to 1.29, $p=<0.001$; AMS-R mean difference 0.46, 95% CI = 0.32 to 0.59, $p=<0.001$). There were no LLS symptom scores at sea level because, by definition, the instrument is not appropriate for use at low altitude prior to ascent. The greatest difference in LLS score was between the morning of the second day and the afternoon of the third day (2.78, 95% CI = 1.53 to 4.03, $p=<0.001$).

Both mean symptom scores and individual scores of many volunteers achieved the criteria for presence of acute mountain sickness during the initial three days of altitude exposure. The mean AMS-C scores exceeded the 0.7 criterion score for presence of AMS on the first evening of altitude exposure (within six hours of ascent) and remained above that criterion score through the morning of the third day of exposure, but mean AMS-R scores did not exceed the 0.6 AMS-R criterion score at any time during the first three days at altitude. The mean LLS scores exceeded the 'original' criterion score for AMS (i.e., 3.0) at every time period during the first three days, but only exceeded the 'revised' criterion score of 5.0 on the morning of the second day.

Based upon the criterion scores, more than half of the volunteer subjects experienced AMS during the first 24 hours of altitude exposure. Thirty of 39 individuals had AMS by AMS-C criterion, an incidence of 77 per 100 individuals exposed. By AMS-R criterion the incidence was less (i.e., 24 of 39 individuals, an incidence of 62 per 100 exposed). Thirty-six individuals had AMS during the first 24 hrs by the original LLS criterion score (an incidence of 92 per 100 individuals exposed), and 31 had AMS using the 'revised' criterion (an incidence of 79 per 100 exposed).

The differences in mean symptom scores between follicular and luteal groups were relatively small. Except for AMS-C on the first day of altitude exposure, the mean scores of the luteal phase group were consistently less than those of the follicular phase group. The mean AMS-C scores for the luteal group dropped below the AMS-C criterion score on the afternoon of the second day of altitude exposure, while the mean scores for the follicular group remained above the criterion during the entire exposure. Similarly, the

Symptom Scores in Women During First 60 Hours at 4300 m



mean LLS scores for the luteal group dropped below the original criterion score on the afternoon of the third day, while the mean scores of the follicular group remained above the criterion for the entire period. The differences between groups were not statistically significant (AMS-C 0.25, 95% CI = 0.00 to 0.49, p=0.234; AMS-R 0.17, 95% CI = 0.05 to 0.29, p=0.103; LLS, 0.22, 95% CI = 0.09 to 0.34, p=0.052), however.

The severity index values calculated from ESQ scores followed the same general pattern as the symptom scores themselves, i.e., symptoms were most severe on the morning of the 2nd day of exposure, then became progressively less intense (Table 8). Although the severity index values were lower in the luteal group in all but one instance (i.e., AMS-R, Day 1 pm), the differences were not statistically significant (AMS-C SI 0.302, 95% CI = -0.033 to 0.638, p=0.077; AMS-R SI 0.144, 95% CI = -0.014 to 0.302, p=0.073).

Table 8. Mean Severity Index for AMS During First 60-Hours Exposure to 4300 m Altitude

Menstrual-cycle Phase	Altitude Exposure				
	Day 1 pm (CI)	Day 2 am (CI)	Day 2 pm (CI)	Day 3 am (CI)	Day 3 pm (CI)
	AMS-C Severity Index				
Follicular	1.174 (0.626 to 1.722) n=23	1.455 (0.802 to 2.107) n=22	0.810 (0.241 to 1.378) n=21	1.0 (0.356 to 1.644) n=21	0.857 (0.373 to 1.341) n=21
Luteal	1.313 (0.706 to 1.919) n=16	1.063 (0.531 to 1.594) n=16	0.688 (0.222 to 1.153) n=16	0.563 (0.227 to 0.898) n=16	0.188 (-0.027 to 0.402) n=16
	AMS-R Severity Index				
Follicular	0.870 (0.599 to 1.140) n=23	0.909 (0.720 to 1.098) n=22	0.750 (0.542 to 0.958) n=20	0.857 (0.596 to 1.118) n=21	0.762 (0.478 to 1.046) n=21
Luteal	0.938 (0.632 to 1.243) n=16	0.688 (0.432 to 0.943) n=16	0.625 (0.295 to 0.955) n=16	0.688 (0.432 to 0.943) n=16	0.500 (0.225 to 0.775) n=16

"CI" indicates 95% confidence interval; "n" is the sample size.
Differences in group size reflects inaccurate prediction of menstrual cycle phase. Differences in sample size within the cycle-phase groups is due to missing or inadequate samples.

The prevalence of AMS (ratio of individuals with AMS compared to total number of individuals exposed to altitude at any one time) based on criterion symptom scores generally peaked on the morning of the second day, then diminished progressively

(Table 8).

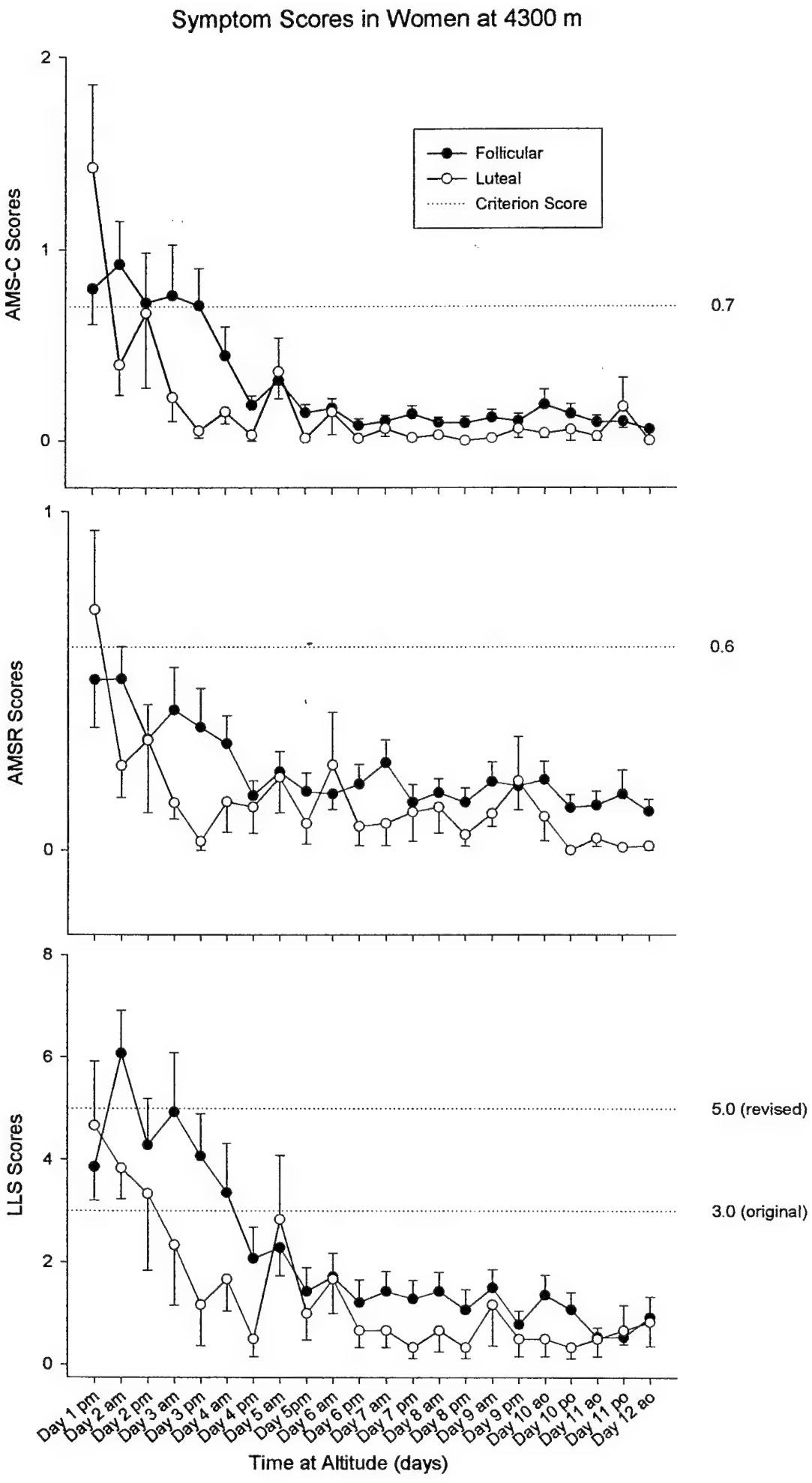
Table 9. Prevalence of Acute Mountain Sickness During First 60-Hours Exposure to 4300 m*

Menstrual-cycle Phase	Day 1 pm	Day 2 am	Day 2 pm	Day 3 am	Day 3 pm
			AMS-C		
Follicular	60.9	54.5	42.9	33.3	33.3
Luteal	50.0	37.5	25.0	31.3	6.3
			AMS-R		
Follicular	39.1	45.5	28.6	23.8	33.3
Luteal	37.5	37.5	12.5	6.3	6.3
			LLS (original criterion)		
Follicular	78.3	95.5	61.9	61.9	61.9
Luteal	56.3	81.3	62.5	62.5	43.8
			LLS (revised criterion)		
Follicular	43.5	72.7	47.6	42.9	38.1
Luteal	50.0	68.7	31.3	50.0	25.0

*Prevalence is the ratio of number of individuals with AMS to the total number of individuals exposed to altitude at any one time expressed as a percent (i.e., number sick for every 100 individuals exposed)

Based upon the ESQ scores, the prevalence of AMS was always lower in the luteal phase group and the effect of cycle phase was statistically significant (AMS-C 15.0, 95% CI = 3.5 to 26.4, p=0.022; AMS-R 14.0, 95% CI = 2.0 to 26.1, p=0.032). The prevalence was not consistently lower using the LLS scores, and the differences were not statistically significant (LLS original 10.6, 95% CI = -2.6 to 23.8, p=0.089; LLS revised 4.0, 95% CI = -9.5 to 17.4, p=0.459).

None of the symptom scores were statistically significantly correlated with estrogen and progesterone AUCs for days 1-3 of altitude exposure. Further, none were correlated with $V_{E\,(rest)}$, $P_{ET}CO_2$ or SaO_2 during the initial three days.


Symptom Scores in Women at 4300 m
AMS-C Scores
2
1
0
Follicular
Luteal
Criterion Score
0.7
AMSR Scores
1
0
0.6
LLS Scores
8
6
4
2
0
5.0 (revised)
3.0 (original)
Day 1 pm
Day 2 am
Day 2 pm
Day 3 am
Day 3 pm
Day 4 am
Day 4 pm
Day 5 am
Day 5pm
Day 6 am
Day 6 pm
Day 7 am
Day 7 pm
Day 8 am
Day 8 pm
Day 9 am
Day 9 pm
Day 10 ao
Day 10 po
Day 11 ao
Day 11 po
Day 12 ao
Time at Altitude (days)

Twelve-day Altitude Exposure

The pattern of symptom scores and AMS defined by those scores in volunteer subjects during 12 days of altitude exposure is suggestive of enhanced acclimatization during the luteal phase, although the effect is not blatantly obvious. Several observations are supportive, however. First, with the exception of evenings on the day of ascent and the 11th day and the mornings of the fifth and sixth days after ascent, the mean symptom scores of the luteal phase group were lower than those of the follicular group (Figure 2). Further, the mean AMS-C and LLS (original criterion) symptom score values for the luteal phase group dropped below their criterion scores ~36 hours before those of the follicular phase group.

Although the mean values for the luteal group symptom scores were usually less than those of the follicular group, the overall effects of menstrual cycle phase were not statistically significant (AMS-C, p=0.234; AMS-R, p=0.194; LLS, p=0.460). There were statistically significant interactions, however, and the confidence intervals for the difference in the overall mean values are consistent with a possible difference between follicular and luteal phase scores (AMS-C 0.17, 95% CI = 0.064 to 0.27, p=0.002; AMS-R 0.09, 95% CI = 0.04 to 0.15, p=0.002; LLS 0.53, 95% CI = 0.6 to 1.0, p=0.028).

Prevalence of AMS, defined as the number experiencing AMS at any one time out of 100 of individuals exposed to 4300 m altitude, using ESQ score criteria was always less in the luteal group compared to the follicular group after the evening of the day of ascent (Table 8). That difference was statistically significant (AMS-C 10.8, 95% CI = 1.02 to 20.63, p=<0.001; AMS-R 14.8, 95% CI = 8.38 to 21.23, p=<0.001). While the prevalence of AMS using LLS score criteria was generally less in the luteal group, the difference was not statistically significant (LLS-original 5.7, 95% CI = -8.38 to 19.59, p=0.411; LLS-revised 1.1, 95% CI = -12.05 to 9.84, p=0.84).

DISCUSSION

The results of this study only partially support the hypothesis that women ascending to high altitude in the luteal phase of their menstrual cycle will have less AMS and/or will have more rapid resolution of AMS symptoms due to stimulation of ventilation by increased endogenous progesterone. The generally lower mean symptom scores and lower prevalence of AMS based upon ESQ scores in the luteal phase supports the hypothesis, but the lack of statistically significant differences between follicular and luteal phase values for symptom scores, severity index scores based upon the ESQ and prevalence based on LLS scores are not supportive. Further, the data do not support the explanatory limb of the hypothesis in that there were no statistically significant differences in measures of resting ventilation and arterial saturation between the cycle phase groups, and a lack of significant correlation between hormone levels and measures of ventilation and AMS. The lack of statistically significant differences between menstrual-cycle phases was previously documented in a sub-sample of the volunteer subjects who participated in this study (Muza

et al., 1997).

Although the lack of statistically significance for many of the measured variables failed to support the study hypothesis, those 'negative' findings cannot be taken as definitive evidence against the hypothesis due to low statistical power associated with the results. *Post hoc* power analyses showed that the power to detect statistical significant differences of the magnitude observed was low, generally below 0.50. The low statistical power probably was a function of several factors including limitations upon the sample size imposed by the study design, relatively imprecise control of altitude exposure and menstrual-cycle phase as independent variables, and possible problems with the precision and validity of the instruments used to measure AMS symptoms.

Because this investigation of AMS in women was a sub-study of the larger project, its design and statistical power were subject to constraints and contingencies imposed by the priorities of that project. Because the overall project involved an α-adrenergic-blockade treatment, volunteer subjects available for this sub-study were limited to the placebo, and untreated arms of the project. In an attempt to increase statistical power, the sample size was increased by including volunteer subjects from all three years of the overall project in the analysis. While this strategy may have increased statistical power, it also added to variability due to differences in exposure conditions between Pikes Peak and the hypobaric chamber and between years at Pikes Peak.

The methods employed to generate the independent variables (i.e., altitude exposure and menstrual-cycle phase) used in this study were imprecise enough as to be significant sources of variability in the data collected. As noted above, differences in altitude exposure conditions between the Pikes Peak laboratory facility and the hypobaric chamber may have affected the magnitude and acuity of the hypobaric-hypoxia stimulus that causes AMS. Those differences include rate of ascent (the rate was much faster in the hypobaric chamber, i.e., minutes vs. hours at Pikes Peak), the range of barometric pressure (the chamber was controlled within ±2 mmHg while ambient atmospheric fluctuations of 8-10 mmHg can occur at Pikes Peak), and the psychological impact of confinement (the chamber is a relatively small [~3600 cubic feet] stainless-steel box that the volunteers cannot leave during altitude exposure, while volunteers at Pikes Peak have access to more than an acre of mountain top outside the laboratory). In addition to the differences between Pikes Peak and the hypobaric chamber, there were some differences in ascent rate and ambient barometric pressure between years at Pikes Peak. However, if those differences had a great effect, they should have caused statistically significant differences between study years, but that was not the case.

This study was designed to standardize the independent variable of menstrual-cycle phase by timing the onset of altitude exposure with phenomena associated with the beginning of the follicular and luteal menstrual-cycle phases. The accuracy of that timing was then confirmed or refuted by *post hoc* analysis of ovarian hormone levels. Major sources of variation from this procedure include the accuracy of the methods used for timing and the inherent variability of menstrual cycles in individuals of the age of the

volunteer subjects. With regard to timing, it is unlikely that volunteer subjects misidentified the onset of their menses as the beginning of their follicular phase. They were more likely to have misread the urine self-test that identified the LH 'surge' which marked the beginning of the luteal phase. There is little definitive information to suggest how often this may have happened, but the commercial ovulation prediction tests used are designed for ease of use and are known to be accurate (Guermandi, et al., 2001; Luciano, et al., 1990), which should have mitigated against this aspect being a major source of variability. However, given the low rate of documented luteal phase in volunteer subjects who were originally assigned to be exposed to altitude in that cycle phase, it is possible that the urine-test prediction method could have been somewhat ineffective in this study.

As alluded to in the "Results" section, the most likely source of variation in menstrual cycle is the inherent high degree of inter- and intra-individual variability of the cycle itself in women the age of the volunteer subjects (Landgren et al., 1980; Vourento et al., 1989). It is very likely that the physiologic stresses of altitude exposure and the psychological stresses associated with travel to Pikes Peak and many of the testing procedures used in the overall project (e.g., exercise testing, vascular catheterization, restricted diet) may have induced abnormal cycles, most likely anovulatory and/or shortened luteal-phase cycles. Some of the volunteer subjects with documented abnormal cycles were classified as being in the follicular phase for purposes of statistical analysis, because low levels of estradiol and progesterone are characteristic of the early follicular phase. Doing so increased the sample size of the follicular versus the luteal cycle-phase groups and may have affected the statistical power, but if increasing levels of ovarian hormones are important for altitude acclimatization, the low levels in these women may have generated increased variability that could have obscured the hypothesis. By the same logic, if high luteal phase hormone levels are important for enhanced acclimatization, the mismatch that was inherent in the study design between the period of maximum hypoxic stress (i.e., the initial 24-48 hours of exposure) and the period of highest circulating ovarian hormone levels (i.e., mid-luteal phase, approximately 7-10 days after the LH surge), may have diminished the chances of detecting any hormone effect.

Another potential source of variation that could affect the results of this study is a possible measurement bias due to the fact that the ESQ criterion scores for the presence of AMS and the symptom severity index were developed by analyzing scores from male volunteer subjects (Sampson et al., 1983). Whether the criterion score and severity index are valid for women has not been specifically investigated, although previously reported studies seem to have operated on the assumption that the instrument is valid for use in women. The original criterion for AMS using LLS scores was set by consensus of a conference of experts in altitude medicine (Roach et al, 1993) and is presumed to be valid for use in women, although its validity has apparently not been formally tested. The revised LLS criterion score suggested by Maggiorini and co-workers (1998) was developed using scores of a mixed group of men and women, and should, therefore, be valid for women. Even if the criterion scores were not valid to identify presence of AMS in women, however, the comparison of the actual scores between cycle phase would still provide evidence to

support or refute the study hypothesis.

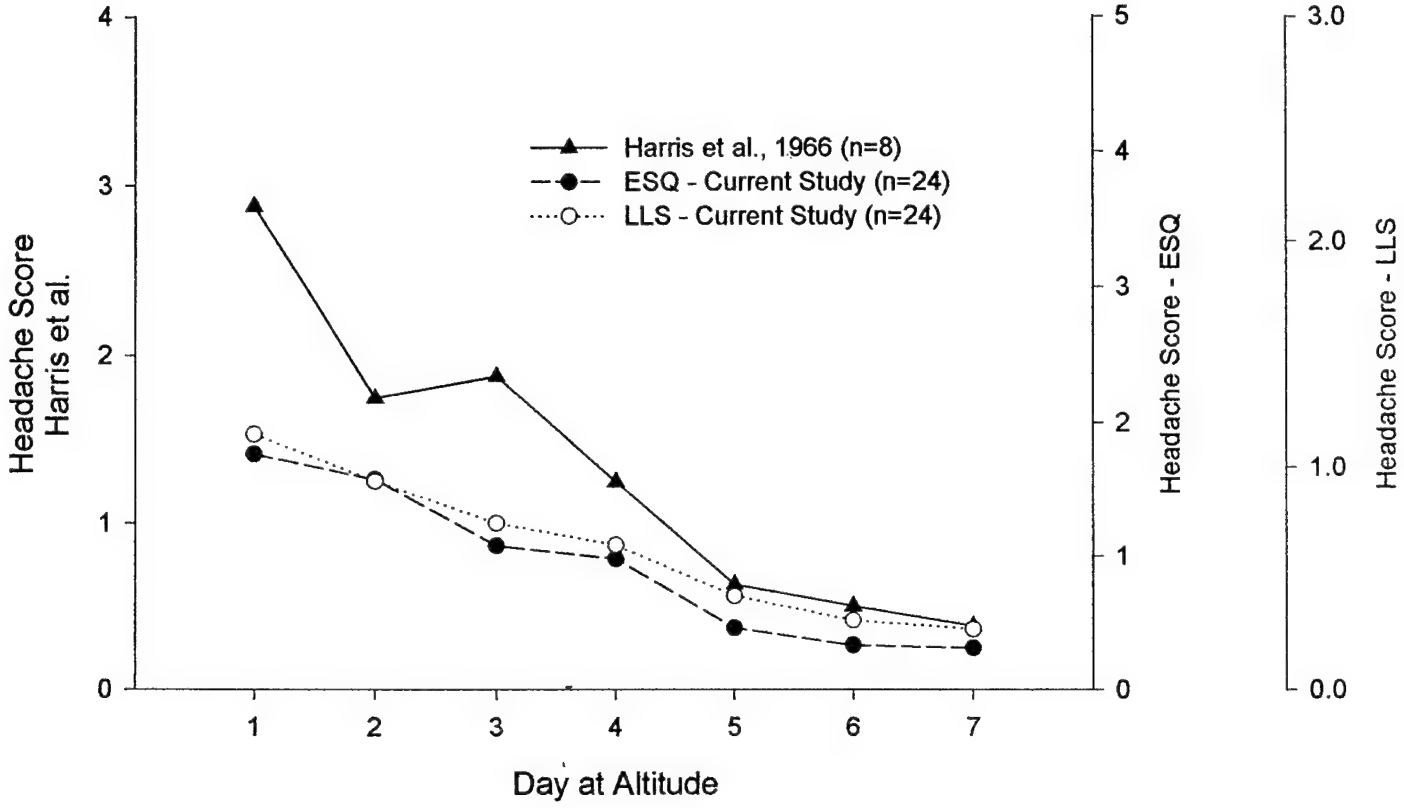
Favorable comparisons of the results of the current study with previously reported studies of AMS in women provides some support for the validity of the findings. First, the overall timing and severity of symptoms documented in the total group of volunteer subjects in the present study closely resembles findings reported for a previous study of unacclimatized, college-aged women exposed to altitude on the summit of Pikes Peak more than 30 years ago (Harris et al, 1966). The similarity in occurrence of AMS observed in both studies (Figure 3), both performed at the same location but widely separated in time, provides good evidence for a repeatable effect that likely represents the normal response of unacclimatized women to 4300 m altitude. However, although Harris and colleagues reported some possible effects of altitude exposure on menstrual cycle in their volunteer subjects, they did not report the reverse possibility that menstrual-cycle may have had effects on AMS and altitude acclimatization.

The absence of unequivocal evidence for a effect of menstrual-cycle phase on AMS symptoms during early altitude exposure is consistent with the findings of Riboni and colleagues (1999) who reported finding no statistically significant effect of menstrual-cycle phase on occurrence of AMS in women exposed to hypobaric hypoxia for eight hours in a hypobaric chamber during both the follicular and the luteal phases of their menstrual cycles using a crossover experimental design. To date, that study has only been reported in abstract form, however, and final assessment of their results must await a full report.

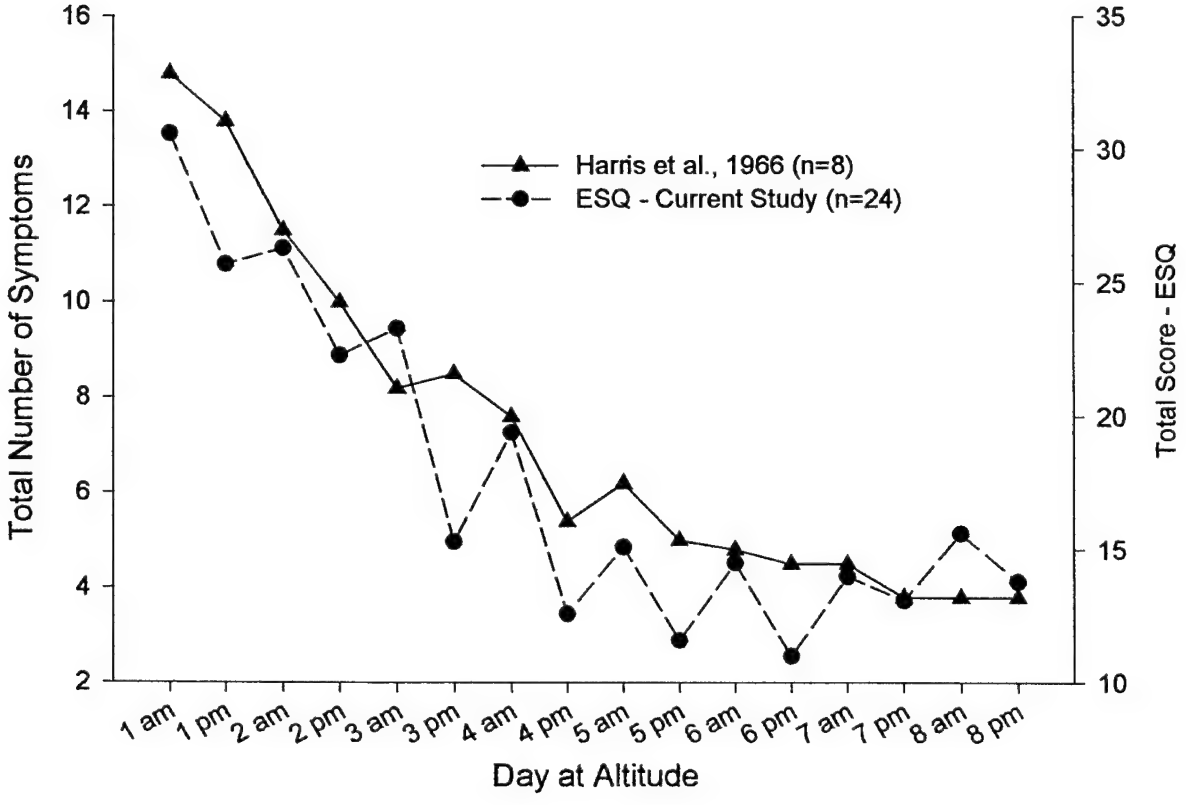
The results of the current study are not sufficiently compelling to either prove or disprove the hypothesis that the hormonal makeup of the luteal cycle phase either pre-acclimatizes women thereby protecting them to some degree from AMS, or increases their rate of acclimatization with the consequent more rapid resolution of symptoms. Even if the hypothesis is correct, the findings are tenuous enough, and the effect size small enough, that the practical implications, as well as any implications for expanding knowledge of the process of acclimatization, are limited. From a practical standpoint, the results could imply that a women ascending to 4300 m altitude at the beginning of the follicular phase of her menstrual cycle might be slightly sicker with AMS for a slightly longer period of time then if she ascended at the beginning of their luteal phase, but that would be an exuberant extrapolation of the findings. Given the study design, a better extrapolation of the results would be that a group of women ascending to 4300 m in their follicular phase might be slightly sicker for slightly longer than a similar group of women ascending in their luteal phase. Given the small effect size and the usually limited period of vulnerability to AMS at this altitude (something on the order of 72 hours), the utility of women in the follicular cycle postponing their ascent for a couple of weeks in order to travel during their luteal phase seems small.

While some demonstrable effects of menstrual-cycle phase were observed, the design and prosecution of this study were not adequate to elucidate the precise mechanisms responsible for those effects. Significantly lacking was sufficient evidence for

Headache in Women on Pikes Peak



Symptoms in Women on Pikes Peak



associated with the luteal phase boosted altitude acclimatization by increasing ventilation, arterial oxygen saturation and O_2 delivery to tissues. The evidence for hormonal effect was insufficient because the design of the study, which was essentially a prospective cohort study, did not provide adequate control of the hormone levels. The problem with control of ovarian hormone levels arose from both the inherent difficulties of accurately predicting the luteal phase of the menstrual cycle and from the somewhat 'fragile' nature of the luteal phase itself. The best design to assess the effect of hormones would be to do a blinded, placebo-controlled, crossover, hormone replacement study in eunuchoid women. Whether such a study is practical or the question important enough to justify doing such a study is debatable.

The results of this study have several potential implications for military deployment to high mountain terrain. First, the effect of cycle phase is small enough that it probably doesn't have to be taken into account for purposes of generating Disease and Non-Battle Injury (DNBI) estimates for planning operations. Second, given that the mean prevalence of AMS in a group of women with a normal distribution of menstrual cycle phases appears to be similar to that in men at the same altitude, female soldiers can probably be deployed to altitude using the same time schedule and ascent rates as used for males. Finally, although this study did not provide direct data on the subject, it is likely that exogenous hormone treatment in the form of combination type oral contraceptives will, if they have any effect at all, minimally enhance altitude acclimatization similar to the luteal menstrual-cycle phase.

CONCLUSIONS

Although the luteal phase of the menstrual cycle is associated with demonstrable reductions in prevalence and severity of AMS in women rapidly deployed to high altitude, the effects are too small to be of much practical significance for either civilian recreational pursuits or military operations. The physiologic mechanisms underlying the decrease in AMS during the luteal phase were not elucidated by the data from this study and will require further investigation. The effects, if any, of exogenous hormones in the form of oral contraceptive therapy (OCT) or reproductive hormone replacement therapy (HRT) in post menopausal women are not known.

RECOMMENDATIONS

Female military personnel can safely be rapidly deployed to high mountain terrain without regard to their menstrual cycle phase. Further research should be done to elucidate the physiologic mechanisms that mediate enhanced acclimatization in the luteal phase as a means to increase understanding of the pathophysiologic mechanisms mediating AMS. Researchers investigating the effects of the luteal phase should consider using exogenous hormone replacement techniques to circumvent the high variability in serum hormone level in normal populations of young, healthy women. Given the likelihood that the luteal phase effects are mediated by ovarian hormones, the potential effects of

exogenous hormone therapy, both OCT and HRT, should be investigated.

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